```
 s anti(w)ctla?and (toleran? or apoptosi?)
         1881056  ANTI
               0  CTLA?AND (TOLERAN?
               0  ANTI(W)CTLA?AND (TOLERAN?
               0  APOPTOSI?)
     S13       0  ANTI(W)CTLA?AND (TOLERAN? OR APOPTOSI?)
? s anti(w)ctla? and (toleran? or apoptosi?)
         1881056  ANTI
           11620  CTLA?
             729  ANTI(W)CTLA?
          502763  TOLERAN?
          507501  APOPTOSI?
     S14     199  ANTI(W)CTLA? AND (TOLERAN? OR APOPTOSI?)
? rd s14
     S15     107  RD S14  (unique items)
? s s15 and py<2000
Processing
           107  S15
      50304892  PY<2000
     S16      16  S15 AND PY<2000
? rd s16
     S17      16  RD S16  (unique items)
? t s17/3/all

 17/3/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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15561659   BIOSIS NO.: 200000279972
The role of CTLA-4 in tolerance induction and T cell differentiation
  in experimental autoimmune encephalomyelitis: I.v. antigen administration
AUTHOR: Ratts Robert B; Arredondo LaChelle R; Bittner Patrice; Perrin Peter
  J; Lovett-Racke Amy E; Racke Michael K (Reprint)
AUTHOR ADDRESS: Department of Neurology, University of Texas Southwestern
  Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, 75235-9036, USA**
  USA
JOURNAL: International Immunology  11 (12): p1889-1895 Dec., 1999
1999
MEDIUM: print
ISSN: 0953-8178
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English


 17/3/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2007 The Thomson Corporation. All rts. reserv.

15561658   BIOSIS NO.: 200000279971
The role of CTLA-4 in tolerance induction and T cell differentiation
  in experimental autoimmune encephalomyelitis: I.p. Antigen administration
AUTHOR: Ratts Robert B; Arredondo LaChelle R; Bittner Patrice; Perrin Peter
  J; Lovett-Racke Amy E; Racke Michael K (Reprint)
AUTHOR ADDRESS: Department of Neurology, University of Texas Southwestern
  Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, 75235-9036, USA**
  USA
JOURNAL: International Immunology  11 (12): p1881-1888 Dec., 1999
1999
MEDIUM: print
ISSN: 0953-8178
DOCUMENT TYPE: Article
```

US 20050196402A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2005/0196402 A1

Gray et al. (43) Pub. Date: Sep. 8, 2005

(54) CTLA4-CY4 FUSION PROTEINS

(75) Inventors: Gary S. Gray, Brookline, MA (US); Jerry Carson, Belmont, MA (US); Kashi Javaherian, Lexington, MA (US); Paul D. Rennert, Holliston, MA (US); Sandra Silver, Boston, MA (US)

Correspondence Address:
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BOSTON, MA 02109 (US)

(73) Assignee: REPLIGEN CORPORATION, Waltham, MA (US)

(21) Appl. No.: 10/985,832

(22) Filed: Nov. 8, 2004

Related U.S. Application Data

(60) Continuation of application No. 10/027,075, filed on Dec. 20, 2001, now abandoned, which is a continuation of application No. 09/227,595, filed on Jan. 8, 1999, now Pat. No. 6,444,792, which is a division of application No. 08/595,590, filed on Feb. 2, 1996, now Pat. No. 6,750,334.

Publication Classification

(51) Int. Cl.[7] A61K 39/395; C07K 16/46

(52) U.S. Cl. 424/178.1; 530/391.1

(57) ABSTRACT

CTLA4-immunoglobulin fusion proteins having modified immunoglobulin constant region-mediated effector functions, and nucleic acids encoding the fusion proteins, are described. The CTLA4-immunoglobulin fusion proteins comprise two components: a first peptide having a CTLA4 activity and a second peptide comprising an immunoglobulin constant region which is modified to reduce at least one constant region-mediated biological effector function relative to a CTLA4-IgG1 fusion protein. The nucleic acids of the invention can be integrated into various expression vectors, which in turn can direct the synthesis of the corresponding proteins in a variety of hosts, particularly eukaryotic cells. The CTLA4-immunoglobulin fusion proteins described herein can be administered to a subject to inhibit an interaction between a CTLA4 ligand (e.g., B7-1 and/or B7-2) on an antigen presenting cell and a receptor for the CTLA4 ligand (e.g., CD28 and/or CTLA4) on the surface of T cells to thereby suppress an immune response in the subject, for example to inhibit transplantation rejection, graft versus host disease or autoimmune responses.

RECORD TYPE: Abstract
LANGUAGE: English

17/3/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15285172 BIOSIS NO.: 200000003485
CTLA-4 blockade reverses CD8+ T cell tolerance to tumor by a CD4+ T cell- and IL-2-dependent mechanism
AUTHOR: Shrikant Protul; Khoruts Alexander; Mescher Matthew F (Reprint)
AUTHOR ADDRESS: Center for Immunology, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, 55455, USA**USA
JOURNAL: Immunity 11 (4): p483-493 Oct., 1999 ***1999***
MEDIUM: print
ISSN: 1074-7613
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

17/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

14161416 BIOSIS NO.: 199799795476
Role of interleukin 12 and costimulators in T cell anergy in vivo
AUTHOR: Van Parijs Luk; Perez Victor L; Biuckians Andre; Maki Robert G; London Cheryl A; Abbas Abul K
AUTHOR ADDRESS: Brigham Women's Hosp., Harvard Med. Sch., LMRC-521 221 Longwood Ave., Boston, MA 02115, USA**USA
JOURNAL: Journal of Experimental Medicine 186 (7): p1119-1128 1997 1997
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

17/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13453822 BIOSIS NO.: 199699087882
CTLA-4 ligation blocks CD28-dependent T cell activation
AUTHOR: Walunas Theresa L; Bakker Christina Y; Bluestone Jeffrey A (Reprint)
AUTHOR ADDRESS: Ben May Inst. Cancer Res., MC1089, Univesity Chicago, 5841 S. Maryland, Chicago, IL 60637, USA**USA
JOURNAL: Journal of Experimental Medicine 183 (6): p2541-2550 1996 1996
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

17/3/6 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07900450 EMBASE No: 1999374235
CTLA-4 blockade reverses CD8sup + T cell tolerance to tumor by a CD4sup + T cell- and IL-2-dependent mechanism
Shrikant P.; Khoruts A.; Mescher M.F.
M.F. Mescher, Center for Immunology, Dept. of Lab. Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455 United States
AUTHOR EMAIL: mesch001@maroon.tc.umn.edu
Immunity (IMMUNITY) (United States) 1999, 11/4 (483-493)
CODEN: IUNIE ISSN: 1074-7613
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 46

17/3/7 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07334769 EMBASE No: 1998196007
Long-term survival of skin allografts induced by donor splenocytes and anti-CD154 antibody in thymectomized mice requires CD4sup + T cells, interferon- gamma, and CTLA4
Markees T.G.; Phillips N.E.; Gordon E.J.; Noelle R.J.; Shultz L.D.; Mordes J.P.; Greiner D.L.; Rossini A.A.
A.A. Rossini, Diabetes Division, Univ. of Massachusetts Med. School, 373 Plantation Street, Worcester, MA 01605 United States
AUTHOR EMAIL: Aldo.Rossini@ummed.edu
Journal of Clinical Investigation (J. CLIN. INVEST.) (United States) 01 JUN 1998, 101/11 (2446-2455)
CODEN: JCINA ISSN: 0021-9738
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 60

17/3/8 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07254566 EMBASE No: 1998127892
CTLA-4 regulates tolerance induction and T cell differentiation in vivo
Walunas T.L.; Bluestone J.A.
Dr. J.A. Bluestone, MC1089, 5841 South Maryland Avenue, Chicago, IL 60637 United States
AUTHOR EMAIL: jbluest@immunology.uchicago.edu
Journal of Immunology (J. IMMUNOL.) (United States) 15 APR 1998, 160/8 (3855-3860)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 35

17/3/9 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

07254541 EMBASE No: 1998127867
T:T antigen presentation by activated murine CD8sup + T cells induces anergy and apoptosis
Chai J.-G.; Bartok I.; Scott D.; Dyson J.; Lechler R.

Dr. R. Lechler, Department of Immunology, Hammersmith Hospital, Imperial College of Sci., Tech./Med., Du Cane Road, London W12 United Kingdom
AUTHOR EMAIL: riechler@rpms.ac.uk
Journal of Immunology (J. IMMUNOL.) (United States) 15 APR 1998, 160/8 (3655-3665)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 65

17/3/10 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2007 Elsevier B.V. All rts. reserv.

07195012 EMBASE No: 1998083489
Cutting edge: CTLA-4 ligation delivers a unique signal to resting human CD4 T cells that inhibits interleukin-2 secretion but allows bcl-X(L) induction
Blair P.J.; Riley J.L.; Levine B.L.; Lee K.P.; Craighead N.; Francomano T.; Perfetto S.J.; Gray G.S.; Carreno B.M.; June C.H.
Dr. C.H. June, Immune Cell Biology Program (061), Naval Medical Research Institute, 8901 Wisconsin Avenue, Bethesda, MD 20889-5607 United States
AUTHOR EMAIL: juneC@nmripo.nmri.nnmc.navy.mil
Journal of Immunology (J. IMMUNOL.) (United States) 1998, 160/1 (12-15)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 27

17/3/11 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 2007 Elsevier B.V. All rts. reserv.

07173182 EMBASE No: 1998055992
Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) regulates the unfolding of autoimmune diabetes
Luhder F.; Hoglund P.; Allison J.P.; Benoist C.; Mathis D.
Dr. D. Mathis, IGBMC, 1 rue Laurent Fries, 67404 Illkirch Cedex France
AUTHOR EMAIL: cbdm@igbmc.u-strasbg.fr
Journal of Experimental Medicine (J. EXP. MED.) (United States) 02 FEB 1998, 187/3 (427-432)
CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32

17/3/12 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

12179813 PMID: 10590254
The role of CTLA-4 in tolerance induction and ttigen administration cell differentiation in experimental autoimmune encephalomyelitis: i. v. antigen administration.
Ratts R B; Arredondo L R; Bittner P; Perrin P J; Lovett-Racke A E; Racke M K
Department of Neurology, Washington University School of Medicine, St Louis, MO 63110, USA.

International immunology (ENGLAND) Dec 1999, 11 (12) p1889-96, ISSN 0953-8178--Print Journal Code: 8916182
Contract/Grant No.: R01-NS-37513; NS; NINDS; R29-AI-43296; AI; NIAID
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

17/3/13 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11937962 PMID: 9763603
Cytotoxic T lymphocyte antigen 4 is induced in the thymus upon in vivo activation and its blockade prevents anti-CD3-mediated depletion of thymocytes.
Cilio C M; Daws M R; Malashicheva A; Sentman C L; Holmberg D
Department for Cell and Molecular Biology, Umea University, S-901 87 Umea, Sweden.
Journal of experimental medicine (UNITED STATES) Oct 5 1998, 188 (7) p1239-46, ISSN 0022-1007--Print Journal Code: 2985109R
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

17/3/14 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11743770 PMID: 9558065
T:T antigen presentation by activated murine CD8+ T cells induces anergy and ***apoptosis*** .
Chai J G; Bartok I; Scott D; Dyson J; Lechler R
Department of Immunology, Hammersmith Hospital, Imperial College of Science, Technology, and Medicine, London, United Kingdom.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Apr 15 1998, 160 (8) p3655-65, ISSN 0022-1767--Print Journal Code: 2985117R
Publishing Model Print
Document type: In Vitro; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

17/3/15 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11739136 PMID: 9551948
CTLA-4 ligation delivers a unique signal to resting human CD4 T cells that inhibits interleukin-2 secretion but allows Bcl-X(L) induction.
Blair P J; Riley J L; Levine B L; Lee K P; Craighead N; Francomano T; Perfetto S J; Gray G S; Carreno B M; June C H
Naval Medical Research Institute, Bethesda, MD 20889-5607, USA.

Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Jan 1 1998, 160 (1) p12-5, ISSN 0022-1767--Print Journal Code: 2985117R
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, Non-P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

17/3/16 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

124229989 CA: 124(17)229989f PATENT
Ligands for induction of antigen specific apoptosis in T cells
INVENTOR(AUTHOR): Gribben, John G.; Freeman, Gordon J.; Nadler, Lee M.; Rennert, Paul; Jellis, Cindy L.; Greenfield, Edward; Gray, Gary S.
LOCATION: USA
ASSIGNEE: Repligen Corp.; Dana Farber Cancer Institute
PATENT: PCT International ; WO 9533770 A1 DATE: 951214
APPLICATION: WO 95US6726 (950602) *US 253783 (940603)
PAGES: 86 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07K-014/705A; C07K-016/28B; A61K-039/395B; A61K-038/17B
DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; DE; DK ; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
? t s17/kwic/all
>>>KWIC option is not available in file(s): 399

17/KWIC/1 (Item 1 from file: 5)
DIALOG(R)File 5:

The role of CTLA-4 in tolerance induction and T cell differentiation in experimental autoimmune encephalomyelitis: I.v. antigen administration
1999

...ABSTRACT: cells and CTLA-4 on T cells have been shown to be important in establishing ***tolerance*** . In the present study, we examined the kinetics of ***tolerance*** induction following i.v. administration of myelin basic protein (MBP) Ac1-11 in mice transgenic...

...node cell (LNC) response 10 days after antigen administration demonstrated an accentuation of i.v. ***tolerance*** induction with ***anti*** - ***CTLA*** -4 blockade. Anergy was induced in splenocytes by i.v. antigen administration as shown by a decrease in MBP-specific proliferation and IL-2 production, and anti-CTLA-4 potentiated this effect. In addition, i.v. antigen plus ***anti*** - ***CTLA*** -4 and complete Freund's adjuvant was not encephalitogenic. Interestingly, i.v. ***tolerance*** (a single injection) did not inhibit experimental autoimmune encephalomyelitis (EAE) and anti-CTLA -4 administration did not alter this phenotype. These results suggest that while the majority of...
...T cells are tolerized by i.v. antigen and that this process is potentiated by anti-CTLA-4 administration, a population of T cells remains that is quite efficient in mediating EAE.
DESCRIPTORS:
MISCELLANEOUS TERMS: ... ***tolerance*** induction

17/KWIC/2 (Item 2 from file: 5)
DIALOG(R)File 5:

The role of CTLA-4 in tolerance induction and T cell differentiation in experimental autoimmune encephalomyelitis: I.p. Antigen administration
1999

...ABSTRACT: that co-stimulation provided by B7 molecules through CTLA-4 is important in establishing peripheral ***tolerance*** . In the present study, we examined the kinetics of tolerance induction and T cell differentiation following i.p. administration of myelin basic protein (MBP) Ac1...

...node cell response after antigen administration demonstrated a dependence on CTLA-4 for i.p. ***tolerance*** induction. Examination of splenocyte responses suggested that i.p. antigen administration induced a Th2 response, which was potentiated by anti-CTLA-4 administration. Interestingly, i.p. ***tolerance*** was able to inhibit the induction of experimental autoimmune encephalomyelitis and anti -CTLA-4 administration did not alter this phenotype, suggesting that CTLA-4 blockade did not block ***tolerance*** induction. Thus, T cell differentiation and the dependence on CTLA-4 for tolerance induction following i.p. antigen administration differs between lymph node and spleen in a model...
DESCRIPTORS:
MISCELLANEOUS TERMS: ... ***tolerance*** induction

17/KWIC/3 (Item 3 from file: 5)

CTLA-4 blockade reverses CD8+ T cell tolerance to tumor by a CD4+ T cell- and IL-2-dependent mechanism
1999

...ABSTRACT: LN and spleen where they exhibit "split anergy" and cannot further proliferate to antigen. Administering ***anti*** - ***CTLA*** -4 mAb early caused sustained OT-1 expansion in the PC, and late administration caused...

17/KWIC/4 (Item 4 from file: 5)

1997

...ABSTRACT: interleukin (IL)-12, a potent inducer of Th1 responses, in regulating this process. T cell ***tolerance*** was induced by the administration of protein antigen without adjuvant in normal mice, and in ...

...from T cell receptor transgenic mice. The administration of IL-12 at the time of tolerance induction stimulates Th1 differentiation, but does not promote antigen-specific T cell proliferation. Conversely, inhibiting...

...differentiation. T cells exposed to tolerogenic antigen in the presence of both IL-12 and anti-CTLA-4 antibody are not energized, and behave identically to T cells which have encountered immunogenic...

...the differentiation of T cells into Th1 effector cells. The combination of IL-12 and anti-CTLA-4 antibody is sufficient to convert a normally tolerogenic stimulus to an immunogenic one.

17/KWIC/5 (Item 5 from file: 5)
DIALOG(R)File 5:(c) 2007 The Thomson Corporation. All rts. reserv.

1996

...ABSTRACT: results demonstrate that the primary effect of CTLA-4 ligation is not the induction of ***apoptosis*** . Instead, CTLA-4 signaling blocks IL-2 production, IL-2 receptor expression, and cell cycle...

...was more pronounced at late (72 h) time points after initial activation. The effects of anti-CTLA-4 mAbs were most apparent in the presence of optimal CD28-mediated co-stimulation consistent...

17/KWIC/6 (Item 1 from file: 73)
DIALOG(R)File 73:(c) 2007 Elsevier B.V. All rts. reserv.

CTLA-4 blockade reverses CD8sup + T cell tolerance to tumor by a CD4sup + T cell- and IL-2-dependent mechanism

...LN and spleen where they exhibit 'split anergy' and cannot further proliferate to antigen. Administering ***anti*** - ***CTLA*** -4 mAb early caused sustained OT-1 expansion in the PC, and late administration caused ...
MEDICAL DESCRIPTORS:
*immunological tolerance
1999

17/KWIC/7 (Item 2 from file: 73)
DIALOG(R)File 73:(c) 2007 Elsevier B.V. All rts. reserv.

...initially depended on the presence of IFN-gamma, CTLA4, and CD4sup + T cells. Addition of ***anti*** - ***CTLA4*** or anti-IFN-gamma mAb to the protocol was associated with prompt graft rejection, whereas...
MEDICAL DESCRIPTORS:
spleen cell; thymectomy; graft rejection--drug therapy--dt; graft rejection --prevention--pc; immunological tolerance; helper cell; t lymphocyte subpopulation; adoptive transfer; immunocompetence; alloimmunity; cytokine production; immunosuppressive treatment; nonhuman; male...
1998

17/KWIC/8 (Item 3 from file: 73)
DIALOG(R)File 73:(c) 2007 Elsevier B.V. All rts. reserv.

CTLA-4 regulates tolerance induction and T cell differentiation in vivo

...expansion, decline, tolerization, and differentiation of T cells following treatment with staphylococcal enterotoxin B (SEB). ***Anti*** - CTLA-4 treatment resulted in increased numbers of SEB-reactive T cells and blockade of subsequent ***tolerance*** induction. Further examination of the SEB-reactive cells from anti-CTLA-4-treated mice demonstrated that both the CD4sup + and CD8sup + Vbeta8sup + T cells produced IL...
MEDICAL DESCRIPTORS:
*cytotoxic t lymphocyte; *b lymphocyte differentiation; *immunological tolerance
1998

17/KWIC/9 (Item 4 from file: 73)

T:T antigen presentation by activated murine CD8sup + T cells induces anergy and apoptosis

...peptide led to nonresponsiveness to Ag rechallenge. This was due to the simultaneous induction of apoptosis, involving approximately 40% of the T cells, and of anergy in the surviving cells. These...

...C6 cells to peptide- pulsed T cells from the same clone induced proliferation but not ***apoptosis*** or anergy. The inhibitory effects of T:T presentation were not due to a lack...

...expression increased, and high levels of CTLA-4 (CD152) expression were induced. Although addition of ***anti*** - ***CTLA*** -4 Ab augmented proliferation in response to soluble peptide, no protection from ***apoptosis*** or anergy was observed. Neither Fas nor TNF-alpha was expressed/produced by the C6...

...T presentation. Taken together, these data suggest that T:T Ag presentation induces anergy and apoptosis in murine CD8sup + T cells and may reflect the regulatory consequences of T:T interactions...
MEDICAL DESCRIPTORS:
clonal anergy; apoptosis; cell survival; cell proliferation; immunostimulation; protein expression; cell interaction; nonhuman; female; mouse; controlled study; animal...
1998

17/KWIC/10 (Item 5 from file: 73)

...down-regulation of T cell responses. Interestingly, while IL-2 production was shut off, inhibitory anti-CTLA-4 mAbs permitted induction and expression of the cell survival gene bcl-X(L). Consistent with this observation, cells remained viable and apoptosis was not detected after CTLA-4 ligation.
1998

17/KWIC/11 (Item 6 from file: 73)

...To determine whether cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is involved, we injected anti-CTLA- 4 mAb into a TCR transgenic model of diabetes at different stages of disease. When injected into young mice, months before they would normally become diabetic, anti-CTLA-4 induced diabetes rapidly and essentially universally; this was not the result of a global...

...more aggressive T cell infiltrate in the pancreatic islets. These effects were only observed if anti-CTLA-4 was injected during a narrow time window, before the initiation of insulitis. Thus, engagement...
MEDICAL DESCRIPTORS:
cytotoxic t lymphocyte; transgenic animal; diabetogenesis; immunological tolerance; immunoregulation; nonhuman; mouse; animal experiment; animal model; animal cell; article; priority journal
1998

17/KWIC/12 (Item 1 from file: 155)
DIALOG(R)File 155:(c) format only 2007 Dialog. All rts. reserv.

The role of CTLA-4 in tolerance induction and ttigen administration cell differentiation in experimental autoimmune encephalomyelitis: i. v. antigen administration.
... ***1999*** ,
... cells and CTLA-4 on T cells have been shown to be important in establishing ***tolerance*** . In the present study, we examined the kinetics of ***tolerance*** induction following i.v. administration of myelin basic protein (MBP) Ac1-11 in mice transgenic...

... node cell (LNC) response 10 days after antigen administration demonstrated an accentuation of i.v. ***tolerance*** induction with ***anti*** - ***CTLA*** -4 blockade. Anergy was induced in splenocytes by i.v. antigen administration as shown by a decrease in MBP-specific proliferation and IL-2 production, and ***anti*** - ***CTLA*** -4 potentiated this effect. In addition, i.v. antigen plus ***anti*** - ***CTLA*** -4 and complete Freund's adjuvant was not encephalitogenic. Interestingly, i.v. tolerance (a single injection) did not inhibit experimental autoimmune encephalomyelitis (EAE) and anti-CTLA -4 administration did not alter this phenotype. These results suggest that while the majority of...
... T cells are tolerized by i.v. antigen and that this process is potentiated by anti-CTLA -4 administration, a population of T cells remains that is quite efficient in mediating EAE.
Descriptors: *Antigens, Differentiation--physiology--PH; *Encephalomyelitis, Autoimmune, Experimental--immunology--IM; *Immune Tolerance; *Immunoconjugates; *Myelin Basic Proteins--administration and dosage--AD; *T-Lymphocytes--physiology--PH

17/KWIC/13 (Item 2 from file: 155)
DIALOG(R)File 155:(c) format only 2007 Dialog. All rts. reserv.

... ***1998*** ,
... CD4+CD8+ double positive cells in fetal thymic organ cultures could also be inhibited by ***anti*** - ***CTLA*** -4 antibodies. Thus, our data provide evidence for a role of CTLA-4 in thymic...
; Animals; Antigens, CD; Apoptosis; Intracellular Signaling Peptides and Proteins; Lymphocyte Activation; Lymphocyte Depletion; Mice; Mice, Inbred C57BL; Protein-Tyrosine...

17/KWIC/14 (Item 3 from file: 155)
DIALOG(R)File 155:(c) format only 2007 Dialog. All rts. reserv.

T:T antigen presentation by activated murine CD8+ T cells induces anergy and ***apoptosis*** .
... ***1998*** ,
... peptide led to nonresponsiveness to Ag rechallenge. This was due to the simultaneous induction of apoptosis, involving approximately 40% of the T cells, and of anergy in the surviving cells. These...

... C6 cells to peptide-pulsed T cells from the same clone induced proliferation but not ***apoptosis*** or anergy. The inhibitory effects of T:T presentation were not due to a lack...

... expression increased, and high levels of CTLA-4 (CD152) expression were induced. Although addition of ***anti*** - ***CTLA*** -4 Ab augmented proliferation in response to soluble peptide, no protection from ***apoptosis*** or anergy was observed. Neither Fas nor TNF-alpha was

expressed/produced by the C6...

... T presentation. Taken together, these data suggest that T:T Ag presentation induces anergy and apoptosis in murine CD8+ T cells and may reflect the regulatory consequences of T:T interactions...
...; ME; Antigens, CD80--metabolism--ME; Antigens, CD86; Antigens, CD95 --metabolism--ME; Antigens, Differentiation--metabolism--ME; Apoptosis%% %--immunology--IM; Clone Cells; H-Y Antigen; Lymphocyte Activation; ***Membrane Glycoproteins--metabolism--ME; Mice; Mice...***

17/KWIC/15 (Item 4 from file: 155)
DIALOG(R)File 155:(c) format only 2007 Dialog. All rts. reserv.

... ***1998*** ,
... down-regulation of T cell responses. Interestingly, while IL-2 production was shut off, inhibitory anti-CTLA-4 mAbs permitted induction and expression of the cell survival gene bcl-X(L). Consistent with this observation, cells remained viable and apoptosis was not detected after CTLA-4 ligation.
? t s17/7/all

17/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15561659 BIOSIS NO.: 200000279972
The role of CTLA-4 in tolerance induction and T cell differentiation in experimental autoimmune encephalomyelitis: I.v. antigen administration
AUTHOR: Ratts Robert B; Arredondo LaChelle R; Bittner Patrice; Perrin Peter J; Lovett-Racke Amy E; Racke Michael K (Reprint)
AUTHOR ADDRESS: Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, 75235-9036, USA** USA
JOURNAL: International Immunology 11 (12): p1889-1895 Dec., 1999
1999
MEDIUM: print
ISSN: 0953-8178
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Interactions between B7 molecules on antigen-presenting cells and CTLA-4 on T cells have been shown to be important in establishing ***tolerance*** . In the present study, we examined the kinetics of ***tolerance*** induction following i.v. administration of myelin basic protein (MBP) Ac1-11 in mice transgenic for a TCR Vbeta8.2 gene derived from an encephalitogenic T cell clone specific for MBP Ac1-11. Examination of the lymph node cell (LNC) response 10 days after antigen administration demonstrated an accentuation of i.v. ***tolerance*** induction with ***anti*** - ***CTLA*** -4 blockade. Anergy was induced in splenocytes by i.v. antigen administration as shown by a decrease in MBP-specific proliferation and IL-2 production, and anti-CTLA -4 potentiated this effect. In addition, i.v. antigen plus ***anti*** - ***CTLA*** -4 and complete Freund's adjuvant was not encephalitogenic. Interestingly, i.v. ***tolerance*** (a single injection) did not inhibit experimental autoimmune encephalomyelitis (EAE) and anti-CTLA -4 administration did not alter this phenotype. These results suggest that while the majority of MBP-specific T cells are tolerized by i.v. antigen and that this process is potentiated by anti-CTLA-4 administration, a population of T cells remains that is quite efficient in mediating EAE.

17/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15561658 BIOSIS NO.: 200000279971
The role of CTLA-4 in tolerance induction and T cell differentiation in experimental autoimmune encephalomyelitis: I.p. Antigen administration
AUTHOR: Ratts Robert B; Arredondo LaChelle R; Bittner Patrice; Perrin Peter J; Lovett-Racke Amy E; Racke Michael K (Reprint)
AUTHOR ADDRESS: Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, 75235-9036, USA** USA
JOURNAL: International Immunology 11 (12): p1881-1888 Dec., 1999
1999
MEDIUM: print
ISSN: 0953-8178
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recent evidence suggests that co-stimulation provided by B7 molecules through CTLA-4 is important in establishing peripheral ***tolerance*** . In the present study, we examined the kinetics of ***tolerance*** induction and T cell differentiation following i.p. administration of myelin basic protein (MBP) Ac1-11 in mice transgenic for a TCR Vbeta8.2 gene derived from an encephalitogenic T cell clone specific for MBP Ac1-11. Examination of the lymph node cell response after antigen administration demonstrated a dependence on CTLA-4 for i.p. ***tolerance*** induction. Examination of splenocyte responses suggested that i.p. antigen administration induced a Th2 response, which was potentiated by ***anti*** - ***CTLA*** -4 administration. Interestingly, i.p. ***tolerance*** was able to inhibit the induction of experimental autoimmune encephalomyelitis and anti-CTLA-4 administration did not alter this phenotype, suggesting that CTLA-4 blockade did not block ***tolerance*** induction. Thus, T cell differentiation and the dependence on CTLA-4 for ***tolerance*** induction following i.p. antigen administration differs between lymph node and spleen in a model of organ-specific autoimmunity.

17/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15285172 BIOSIS NO.: 200000003485
CTLA-4 blockade reverses CD8+ T cell tolerance to tumor by a CD4+ T cell- and IL-2-dependent mechanism
AUTHOR: Shrikant Protul; Khoruts Alexander; Mescher Matthew F (Reprint)
AUTHOR ADDRESS: Center for Immunology, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, 55455, USA**USA
JOURNAL: Immunity 11 (4): p483-493 Oct., 1999 ***1999***
MEDIUM: print
ISSN: 1074-7613
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A tumor-specific CD8+ T cell response was studied using adoptive transfer of OT-I TCR transgenic cells. Upon i.p. challenge with E.G7 tumor, OT-I cells undergo CD4+ T cell-independent expansion at the tumor

site and develop lytic function. Before tumor elimination, however, they leave the peritoneal cavity (PC) and appear in the LN and spleen where they exhibit "split anergy" and cannot further proliferate to antigen. Administering anti-CTLA-4 mAb early caused sustained OT-1 expansion in the PC, and late administration caused the OT-I cells to return to the PC and further expand; in both cases, tumor was controlled. These effects required CD4+ T cells and IL-2 and appear to result from reversal of the nonresponsive state of the CD8+ T cells.

17/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

14161416 BIOSIS NO.: 199799795476
Role of interleukin 12 and costimulators in T cell anergy in vivo
AUTHOR: Van Parijs Luk; Perez Victor L; Biuckians Andre; Maki Robert G; London Cheryl A; Abbas Abul K
AUTHOR ADDRESS: Brigham Women's Hosp., Harvard Med. Sch., LMRC-521 221 Longwood Ave., Boston, MA 02115, USA**USA
JOURNAL: Journal of Experimental Medicine 186 (7): p1119-1128 1997
1997
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The induction of T cell anergy in vivo is thought to result from antigen recognition in the absence of co-stimulation and inflammation, and is associated with a block in T cell proliferation and Th1 differentiation. Here we have examined the role of interleukin (IL)-12, a potent inducer of Th1 responses, in regulating this process. T cell tolerance was induced by the administration of protein antigen without adjuvant in normal mice, and in recipients of adoptively transferred T cells from T cell receptor transgenic mice. The administration of IL-12 at the time of tolerance induction stimulates Th1 differentiation, but does not promote antigen-specific T cell proliferation. Conversely, inhibiting CTLA-4 engagement during anergy induction reverses the block in T cell proliferation, but does not promote fun Th1 differentiation. T cells exposed to tolerogenic antigen in the presence of both IL-12 and anti-CTLA-4 antibody are not energized, and behave identically to T cells which have encountered immunogenic antigen. These. results suggest that two processes contribute to the induction of anergy in vivo; CTLA-4 engagement, which leads to a block in the ability of T cells to proliferate to antigen, and the absence of a prototypic inflammatory cytokine, IL-12, which prevents the differentiation of T cells into Th1 effector cells. The combination of IL-12 and anti-CTLA-4 antibody is sufficient to convert a normally tolerogenic stimulus to an immunogenic one.

17/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13453822 BIOSIS NO.: 199699087882
CTLA-4 ligation blocks CD28-dependent T cell activation
AUTHOR: Walunas Theresa L; Bakker Christina Y; Bluestone Jeffrey A (Reprint)
AUTHOR ADDRESS: Ben May Inst. Cancer Res., MC1089, Univesity Chicago, 5841 S. Maryland, Chicago, IL 60637, USA**USA
JOURNAL: Journal of Experimental Medicine 183 (6): p2541-2550 1996

1996
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CTLA-4 is a CD28 homologue believed to be a negative regulator of T cell function. However, the mechanism of this downregulatory activity is not well understood. The present study was designed to examine the effect of CTLA-4 ligation on cytokine production, cell survival, and cell cycle progression. The results demonstrate that the primary effect of CTLA-4 ligation is not the induction of ***apoptosis*** . Instead, CTLA-4 signaling blocks IL-2 production, IL-2 receptor expression, and cell cycle progression of activated T cells. Moreover, the effect of CTLA-4 signaling was manifested after initial T cell activation. Inhibition of IL-2 receptor expression and cell cycle progression was more pronounced at late (72 h) time points after initial activation. The effects of anti-CTLA-4 mAbs were most apparent in the presence of optimal CD28-mediated co-stimulation consistent with the finding that CTLA-4 upregulation was CD28-dependent. Finally, the addition of exogenous IL-2 to the cultures restored IL-2 receptor expression and T cell proliferation. These results suggest that CTLA-4 signaling does not regulate cell survival or responsiveness to IL-2, but does inhibit CD28-dependent IL-2 production.

17/7/6 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07900450 EMBASE No: 1999374235
CTLA-4 blockade reverses CD8sup + T cell tolerance to tumor by a CD4sup + T cell- and IL-2-dependent mechanism
Shrikant P.; Khoruts A.; Mescher M.F.
M.F. Mescher, Center for Immunology, Dept. of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455 United States
AUTHOR EMAIL: mesch001@maroon.tc.umn.edu
Immunity (IMMUNITY) (United States) 1999, 11/4 (483-493)
CODEN: IUNIE ISSN: 1074-7613
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 46

A tumor-specific CD8sup + T cell response was studied using adoptive transfer of OT-I TCR transgenic cells. Upon i.p. challenge with E.G7 tumor, OT-I cells undergo CD4sup + T cell-independent expansion at the tumor site and develop lytic function. Before tumor elimination, however, they leave the peritoneal cavity (PC) and appear in the LN and spleen where they exhibit 'split anergy' and cannot further proliferate to antigen. Administering anti- CTLA-4 mAb early caused sustained OT-1 expansion in the PC, and late administration caused the OT-I cells to return to the PC and further expand; in both cases, tumor was controlled. These effects required CD4sup + T cells and IL-2 and appear to result from reversal of the nonresponsive state of the CD8sup + T cells.

17/7/7 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07334769 EMBASE No: 1998196007
Long-term survival of skin allografts induced by donor splenocytes and

anti-CD154 antibody in thymectomized mice requires CD4sup + T cells, interferon- gamma, and CTLA4

Markees T.G.; Phillips N.E.; Gordon E.J.; Noelle R.J.; Shultz L.D.; Mordes J.P.; Greiner D.L.; Rossini A.A.

A.A. Rossini, Diabetes Division, University of Massachusetts Med. School, 373 Plantation Street, Worcester, MA 01605 United States

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Journal of Clinical Investigation (J. CLIN. INVEST.) (United States) 01 JUN 1998, 101/11 (2446-2455)

CODEN: JCINA ISSN: 0021-9738

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 60

Treatment of C57BL/6 mice with one transfusion of BALB/c spleen cells and anti-CD154 (anti-CD40-ligand) antibody permits BALB/c islet grafts to survive indefinitely and BALB/c skin grafts to survive for ~ 50 d without further intervention. The protocol induces long-term allograft survival, but the mechanism is unknown. We now report: (a) addition of thymectomy to the protocol permitted skin allografts to survive for > 100 d, suggesting that graft rejection in euthymic mice results from thymic export of alloreactive T cells. (b) Clonal deletion is not the mechanism of underlying long-term graft survival, as recipient thymectomized mice were immunocompetent and harbor alloreactive T cells. (c) Induction of skin allograft acceptance initially depended on the presence of IFN-gamma, CTLA4, and CD4sup + T cells. Addition of ***anti*** - ***CTLA4*** or anti-IFN-gamma mAb to the protocol was associated with prompt graft rejection, whereas anti-IL-4 mAb had no effect. The role of IFN-gamma was confirmed using knockout mice. (d) Graft survival was associated with the absence of IFN-gamma in the graft. (e) Long-term graft maintenance required the continued presence of CD4sup + T cells. The results suggest that, with modification, our short-term protocol may yield a procedure for the induction of long-term graft survival without prolonged immunosuppression.

17/7/8 (Item 3 from file: 73)

DIALOG(R)File 73:EMBASE

07254566 EMBASE No: 1998127892

CTLA-4 regulates tolerance induction and T cell differentiation in vivo

Walunas T.L.; Bluestone J.A.

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Journal of Immunology (J. IMMUNOL.) (United States) 15 APR 1998, 160/8 (3855-3860)

CODEN: JOIMA ISSN: 0022-1767

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 35

Cytotoxic T lymphocyte Ag-4 (CTLA-4; CD152) is an important T cell regulatory molecule. In vitro experiments have shown that the blockade of signals through CTLA-4 augments T cell expansion, while CTLA-4 cross-linking results in decreased T cell proliferation due to decreased IL-2 production. However, less is known about the role of CTLA-4 in regulating an ongoing immune response. In this study, we examined the role of CTLA-4 in the expansion, decline, tolerization, and differentiation of T cells following treatment with staphylococcal enterotoxin B (SEB). Anti-CTLA-4 treatment resulted in increased numbers of

SEB-reactive T cells and blockade of subsequent ***tolerance*** induction. Further examination of the SEB-reactive cells from anti-CTLA -4-treated mice demonstrated that both the CD4sup + and CD8sup + Vbeta8sup + T cells produced IL-4, providing evidence that not only do signals through CTLA-4 regulate T cell-tolerizing events, but they also play an important role in the differentiation of T cells in vivo.

17/7/9 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

07254541 EMBASE No: 1998127867
T:T antigen presentation by activated murine CD8sup + T cells induces anergy and apoptosis
Chai J.-G.; Bartok I.; Scott D.; Dyson J.; Lechler R.
Dr. R. Lechler, Department of Immunology, Hammersmith Hospital, Imperial College of Sci., Tech./Med., Du Cane Road, London W12 United Kingdom
AUTHOR EMAIL: riechler@rpms.ac.uk
Journal of Immunology (J. IMMUNOL.) (United States) 15 APR 1998, 160/8 (3655-3665)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 65

Using an IL-2-secreting, noncytolytic, H-Y-specific, CD8sup + T cell clone, the functional consequences of Ag presentation by T cells to T cells were investigated. Incubation of the T cells with H-Y-soluble peptide led to nonresponsiveness to Ag rechallenge. This was due to the simultaneous induction of apoptosis, involving approximately 40% of the T cells, and of anergy in the surviving cells. These effects were strictly dependent upon bidirectional T:T presentation, in that exposure of C6 cells to peptide- pulsed T cells from the same clone induced proliferation but not ***apoptosis*** or anergy. The inhibitory effects of T:T presentation were not due to a lack of costimulation, since the T cells expressed levels of CD80 and CD86 higher than those detected on cultured dendritic cells and equipped them to function as efficient APCs for primary CD8sup + T cell responses. Following incubation with soluble peptide, CD80 expression increased, and high levels of CTLA-4 (CD152) expression were induced. Although addition of anti-CTLA-4 Ab augmented proliferation in response to soluble peptide, no protection from apoptosis or anergy was observed. Neither Fas nor TNF-alpha was expressed/produced by the C6 cells, and coligation of MHC class I molecules and TCR failed to reproduce the effects of T:T presentation. Taken together, these data suggest that T:T Ag presentation induces anergy and apoptosis in murine CD8sup + T cells and may reflect the regulatory consequences of T:T interactions in the course of clonal expansion in vivo.

17/7/10 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

07195012 EMBASE No: 1998083489
Cutting edge: CTLA-4 ligation delivers a unique signal to resting human CD4 T cells that inhibits interleukin-2 secretion but allows bcl-X(L) induction
Blair P.J.; Riley J.L.; Levine B.L.; Lee K.P.; Craighead N.; Francomano T.; Perfetto S.J.; Gray G.S.; Carreno B.M.; June C.H.
Dr. C.H. June, Immune Cell Biology Program (061), Naval Medical Research Institute, 8901 Wisconsin Avenue, Bethesda, MD 20889-5607 United States

AUTHOR EMAIL: juneC@nmripo.nmri.nnmc.navy.mil
Journal of Immunology (J. IMMUNOL.) (United States) 1998, 160/1 (12-15)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 27

We have assessed the functional effects of a panel of CTLA-4 mAbs on resting human CD4sup + T cells. Our results demonstrate that some CTLA-4 mAbs can inhibit proliferative responses of resting CD4sup + cells and cell cycle transition from Ginf 0 to Ginf 1. The inhibitory effects of CTLA-4 were evident within 4 h, at a time when cell surface CTLA-4 expression remained undetectable. Other CTLA-4 mAbs had no detectable inhibitory effects, indicating that binding of Ab to CTLA-4 alone is not sufficient to mediate down-regulation of T cell responses. Interestingly, while IL-2 production was shut off, inhibitory anti-CTLA-4 mAbs permitted induction and expression of the cell survival gene bcl-X(L). Consistent with this observation, cells remained viable and apoptosis was not detected after CTLA-4 ligation.

17/7/11 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

07173182 EMBASE No: 1998055992
Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) regulates the unfolding of autoimmune diabetes
Luhder F.; Hoglund P.; Allison J.P.; Benoist C.; Mathis D.
Dr. D. Mathis, IGBMC, 1 rue Laurent Fries, 67404 Illkirch Cedex France
AUTHOR EMAIL: cbdm@igbmc.u-strasbg.fr
Journal of Experimental Medicine (J. EXP. MED.) (United States) 02 FEB 1998, 187/3 (427-432)
CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32

Evidence has been accumulating that shows that insulin-dependent diabetes is subject to immunoregulation. To determine whether cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is involved, we injected anti-CTLA- 4 mAb into a TCR transgenic model of diabetes at different stages of disease. When injected into young mice, months before they would normally become diabetic, anti-CTLA-4 induced diabetes rapidly and essentially universally; this was not the result of a global activation of T lymphocytes, but did reflect a much more aggressive T cell infiltrate in the pancreatic islets. These effects were only observed if anti-CTLA-4 was injected during a narrow time window, before the initiation of insulitis. Thus, engagement of CTLA-4 at the time when potentially diabetogenic T cells are first activated is a pivotal event; if engagement is permitted, invasion of the islets occurs, but remains quite innocuous for months, if not, insulitis is much more aggressive, and diabetes quickly ensues.

17/7/12 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12179813 PMID: 10590254
The role of CTLA-4 in tolerance induction and ttigen administration

cell differentiation in experimental autoimmune encephalomyelitis: i. v. antigen administration.

Ratts R B; Arredondo L R; Bittner P; Perrin P J; Lovett-Racke A E; Racke M K

Department of Neurology, Washington University School of Medicine, St Louis, MO 63110, USA.

International immunology (ENGLAND) Dec 1999, 11 (12) p1889-96, ISSN 0953-8178--Print Journal Code: 8916182

Contract/Grant Number: R01-NS-37513; NS; NINDS; R29-AI-43296; AI; NIAID

Publishing Model Print

Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Interactions between B7 molecules on antigen-presenting cells and CTLA-4 on T cells have been shown to be important in establishing ***tolerance*** . In the present study, we examined the kinetics of tolerance induction following i.v. administration of myelin basic protein (MBP) Ac1-11 in mice transgenic for a TCR V(beta)8.2 gene derived from an encephalitogenic T cell clone specific for MBP Ac1-11. Examination of the lymph node cell (LNC) response 10 days after antigen administration demonstrated an accentuation of i.v. ***tolerance*** induction with ***anti*** - ***CTLA*** -4 blockade. Anergy was induced in splenocytes by i.v. antigen administration as shown by a decrease in MBP-specific proliferation and IL-2 production, and ***anti*** - ***CTLA*** -4 potentiated this effect. In addition, i.v. antigen plus anti-CTLA-4 and complete Freund's adjuvant was not encephalitogenic. Interestingly, i.v. ***tolerance*** (a single injection) did not inhibit experimental autoimmune encephalomyelitis (EAE) and ***anti*** - ***CTLA*** -4 administration did not alter this phenotype. These results suggest that while the majority of MBP-specific T cells are tolerized by i.v. antigen and that this process is potentiated by anti-CTLA -4 administration, a population of T cells remains that is quite efficient in mediating EAE.

Record Date Created: 20000124

Record Date Completed: 20000124

17/7/13 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11937962 PMID: 9763603

Cytotoxic T lymphocyte antigen 4 is induced in the thymus upon in vivo activation and its blockade prevents anti-CD3-mediated depletion of thymocytes.

Cilio C M; Daws M R; Malashicheva A; Sentman C L; Holmberg D

Department for Cell and Molecular Biology, Umea University, S-901 87 Umea, Sweden.

Journal of experimental medicine (UNITED STATES) Oct 5 1998, 188 (7) p1239-46, ISSN 0022-1007--Print Journal Code: 2985109R

Publishing Model Print

Document type: Journal Article; Research Support, Non-U.S. Gov't

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

The development of a normal T cell repertoire in the thymus is dependent on the interplay between signals mediating cell survival (positive selection) and cell death (negative selection or death by neglect). Although the CD28 costimulatory molecule has been implicated in this process, it has been difficult to establish a role for the other major

costimulatory molecule, cytotoxic T lymphocyte antigen (CTLA)-4. Here we report that in vivo stimulation through the T cell receptor (TCR)-CD3 complex induces expression of CTLA-4 in thymocytes and leads to the association of CTLA-4 with the SH2 domain-containing phosphatase (SHP)-2 tyrosine phosphatase. Moreover, intrathymic CTLA-4 blockade dramatically inhibits anti-CD3-mediated depletion of CD4+CD8+ double positive immature thymocytes. Similarly, anti-CD3-mediated depletion of CD4+CD8+ double positive cells in fetal thymic organ cultures could also be inhibited by ***anti*** - ***CTLA*** -4 antibodies. Thus, our data provide evidence for a role of CTLA-4 in thymic selection and suggest a novel mechanism contributing to the regulation of TCR-mediated selection of T cell repertoires.

Record Date Created: 19981116

Record Date Completed: 19981116

17/7/14 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

11743770 PMID: 9558065

T:T antigen presentation by activated murine CD8+ T cells induces anergy and ***apoptosis*** .

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Department of Immunology, Hammersmith Hospital, Imperial College of Science, Technology, and Medicine, London, United Kingdom.

Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Apr 15 1998, 160 (8) p3655-65, ISSN 0022-1767--Print Journal Code: 2985117R

Publishing Model Print

Document type: In Vitro; Journal Article; Research Support, Non-U.S. Gov't

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Using an IL-2-secreting, noncytolytic, H-Y-specific, CD8+ T cell clone, the functional consequences of Ag presentation by T cells to T cells were investigated. Incubation of the T cells with H-Y-soluble peptide led to nonresponsiveness to Ag rechallenge. This was due to the simultaneous induction of apoptosis, involving approximately 40% of the T cells, and of anergy in the surviving cells. These effects were strictly dependent upon bidirectional T:T presentation, in that exposure of C6 cells to peptide-pulsed T cells from the same clone induced proliferation but not ***apoptosis*** or anergy. The inhibitory effects of T:T presentation were not due to a lack of costimulation, since the T cells expressed levels of CD80 and CD86 higher than those detected on cultured dendritic cells and equipped them to function as efficient APCs for primary CD8+ T cell responses. Following incubation with soluble peptide, CD80 expression increased, and high levels of CTLA-4 (CD152) expression were induced. Although addition of anti-CTLA-4 Ab augmented proliferation in response to soluble peptide, no protection from apoptosis or anergy was observed. Neither Fas nor TNF-alpha was expressed/produced by the C6 cells, and coligation of MHC class I molecules and TCR failed to reproduce the effects of T:T presentation. Taken together, these data suggest that T:T Ag presentation induces anergy and apoptosis in murine CD8+ T cells and may reflect the regulatory consequences of T:T interactions in the course of clonal expansion in vivo.

Record Date Created: 19980504

Record Date Completed: 19980504

17/7/15 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

11739136 PMID: 9551948
CTLA-4 ligation delivers a unique signal to resting human CD4 T cells that inhibits interleukin-2 secretion but allows Bcl-X(L) induction.
Blair P J; Riley J L; Levine B L; Lee K P; Craighead N; Francomano T; Perfetto S J; Gray G S; Carreno B M; June C H
Naval Medical Research Institute, Bethesda, MD 20889-5607, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Jan 1 1998, 160 (1) p12-5, ISSN 0022-1767--Print Journal Code: 2985117R
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, Non-P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We have assessed the functional effects of a panel of CTLA-4 mAbs on resting human CD4+ T cells. Our results demonstrate that some CTLA-4 mAbs can inhibit proliferative responses of resting CD4+ cells and cell cycle transition from G0 to G1. The inhibitory effects of CTLA-4 were evident within 4 h, at a time when cell surface CTLA-4 expression remained undetectable. Other CTLA-4 mAbs had no detectable inhibitory effects, indicating that binding of Ab to CTLA-4 alone is not sufficient to mediate down-regulation of T cell responses. Interestingly, while IL-2 production was shut off, inhibitory anti-CTLA-4 mAbs permitted induction and expression of the cell survival gene bcl-X(L). Consistent with this observation, cells remained viable and apoptosis was not detected after CTLA-4 ligation.
Record Date Created: 19980507
Record Date Completed: 19980507

17/7/16 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

124229989 CA: 124(17)229989f PATENT
Ligands for induction of antigen specific apoptosis in T cells
INVENTOR(AUTHOR): Gribben, John G.; Freeman, Gordon J.; Nadler, Lee M.; Rennert, Paul; Jellis, Cindy L.; Greenfield, Edward; Gray, Gary S.
LOCATION: USA
ASSIGNEE: Repligen Corp.; Dana Farber Cancer Institute
PATENT: PCT International ; WO 9533770 A1 DATE: 951214
APPLICATION: WO 95US6726 (950602) *US 253783 (940603)
PAGES: 86 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07K-014/705A; C07K-016/28B; A61K-039/395B; A61K-038/17B
DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; DE; DK ; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA215003 Immunochemistry
IDENTIFIERS: T cell antigen specific apoptosis ligand, CTLA4 monoclonal antibody T cell apoptosis, graft rejection autoimmune bone marrow transplant
DESCRIPTORS:
Lymphocyte,T-cell...
apoptosis; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Animal cell line...
B lymphoblastoid; monoclonal anti-CTLA4 antibodies and fragments and

CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune disease
Lymphoblast,B-cell...
cell line; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Antibodies...
chimeric or humanized; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune di
Proteins,specific or class, fusion products...
CTLA4-containing; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Antigens,CTLA-4 (cytotoxic T-lymphocyte-activating, 4)...
ligand; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Allergens... Allergy... Antibodies,monoclonal... Antigen receptors,TCR (T-cell antigen receptor)... Antigens... Antigens,auto-... Antigens,B 7.2 ... Antigens,B7/BB-1... Antigens,CD28... Antigens,CD3... Apoptosis... Autoimmune disease... Bone marrow,transplant... Lymphokine and cytokine receptors,interleukin 2... Lymphokines and Cytokines,interleukin 2... Lymphokines and Cytokines,T-cell growth factor... Receptors,interleukin 2 ... Receptors,TCR (T-cell antigen receptor)... Transplant and Transplantation,graft-vs.-host reaction...
monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Transplant and Transplantation...
rejection; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
CAS REGISTRY NUMBERS:
174777-52-7 174777-53-8 monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
?

? t s17/7/all

17/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15561659 BIOSIS NO.: 200000279972
The role of CTLA-4 in tolerance induction and T cell differentiation in experimental autoimmune encephalomyelitis: I.v. antigen administration
AUTHOR: Ratts Robert B; Arredondo LaChelle R; Bittner Patrice; Perrin Peter J; Lovett-Racke Amy E; Racke Michael K (Reprint)
AUTHOR ADDRESS: Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, 75235-9036, USA** USA
JOURNAL: International Immunology 11 (12): p1889-1895 Dec., 1999
1999
MEDIUM: print
ISSN: 0953-8178
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Interactions between B7 molecules on antigen-presenting cells and CTLA-4 on T cells have been shown to be important in establishing ***tolerance*** . In the present study, we examined the kinetics of ***tolerance*** induction following i.v. administration of myelin basic protein (MBP) Ac1-11 in mice transgenic for a TCR Vbeta8.2 gene derived from an encephalitogenic T cell clone specific for MBP Ac1-11. Examination of the lymph node cell (LNC) response 10 days after antigen administration demonstrated an accentuation of i.v. ***tolerance*** induction with ***anti*** - ***CTLA*** -4 blockade. Anergy was induced in splenocytes by i.v. antigen administration as shown by a decrease in MBP-specific proliferation and IL-2 production, and anti-CTLA -4 potentiated this effect. In addition, i.v. antigen plus ***anti*** - ***CTLA*** -4 and complete Freund's adjuvant was not encephalitogenic. Interestingly, i.v. ***tolerance*** (a single injection) did not inhibit experimental autoimmune encephalomyelitis (EAE) and anti-CTLA -4 administration did not alter this phenotype. These results suggest that while the majority of MBP-specific T cells are tolerized by i.v. antigen and that this process is potentiated by anti-CTLA-4 administration, a population of T cells remains that is quite efficient in mediating EAE.

17/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15561658 BIOSIS NO.: 200000279971
The role of CTLA-4 in tolerance induction and T cell differentiation in experimental autoimmune encephalomyelitis: I.p. Antigen administration
AUTHOR: Ratts Robert B; Arredondo LaChelle R; Bittner Patrice; Perrin Peter J; Lovett-Racke Amy E; Racke Michael K (Reprint)
AUTHOR ADDRESS: Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX, 75235-9036, USA** USA
JOURNAL: International Immunology 11 (12): p1881-1888 Dec., 1999
1999
MEDIUM: print
ISSN: 0953-8178
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Recent evidence suggests that co-stimulation provided by B7 molecules through CTLA-4 is important in establishing peripheral ***tolerance*** . In the present study, we examined the kinetics of ***tolerance*** induction and T cell differentiation following i.p. administration of myelin basic protein (MBP) Ac1-11 in mice transgenic for a TCR Vbeta8.2 gene derived from an encephalitogenic T cell clone specific for MBP Ac1-11. Examination of the lymph node cell response after antigen administration demonstrated a dependence on CTLA-4 for i.p. ***tolerance*** induction. Examination of splenocyte responses suggested that i.p. antigen administration induced a Th2 response, which was potentiated by ***anti*** - ***CTLA*** -4 administration. Interestingly, i.p. ***tolerance*** was able to inhibit the induction of experimental autoimmune encephalomyelitis and anti-CTLA-4 administration did not alter this phenotype, suggesting that CTLA-4 blockade did not block ***tolerance*** induction. Thus, T cell differentiation and the dependence on CTLA-4 for ***tolerance*** induction following i.p. antigen administration differs between lymph node and spleen in a model of organ-specific autoimmunity.

17/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

15285172 BIOSIS NO.: 200000003485
CTLA-4 blockade reverses CD8+ T cell tolerance to tumor by a CD4+ T cell- and IL-2-dependent mechanism
AUTHOR: Shrikant Protul; Khoruts Alexander; Mescher Matthew F (Reprint)
AUTHOR ADDRESS: Center for Immunology, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, 55455, USA**USA
JOURNAL: Immunity 11 (4): p483-493 Oct., 1999 ***1999***
MEDIUM: print
ISSN: 1074-7613
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A tumor-specific CD8+ T cell response was studied using adoptive transfer of OT-I TCR transgenic cells. Upon i.p. challenge with E.G7 tumor, OT-I cells undergo CD4+ T cell-independent expansion at the tumor site and develop lytic function. Before tumor elimination, however, they leave the peritoneal cavity (PC) and appear in the LN and spleen where they exhibit "split anergy" and cannot further proliferate to antigen. Administering anti-CTLA-4 mAb early caused sustained OT-1 expansion in the PC, and late administration caused the OT-I cells to return to the PC and further expand; in both cases, tumor was controlled. These effects required CD4+ T cells and IL-2 and appear to result from reversal of the nonresponsive state of the CD8+ T cells.

17/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

14161416 BIOSIS NO.: 199799795476
Role of interleukin 12 and costimulators in T cell anergy in vivo
AUTHOR: Van Parijs Luk; Perez Victor L; Biuckians Andre; Maki Robert G; London Cheryl A; Abbas Abul K
AUTHOR ADDRESS: Brigham Women's Hosp., Harvard Med. Sch., LMRC-521 221 Longwood Ave., Boston, MA 02115, USA**USA

JOURNAL: Journal of Experimental Medicine 186 (7): p1119-1128 1997
1997
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The induction of T cell anergy in vivo is thought to result from antigen recognition in the absence of co-stimulation and inflammation, and is associated with a block in T cell proliferation and Th1 differentiation. Here we have examined the role of interleukin (IL)-12, a potent inducer of Th1 responses, in regulating this process. T cell tolerance was induced by the administration of protein antigen without adjuvant in normal mice, and in recipients of adoptively transferred T cells from T cell receptor transgenic mice. The administration of IL-12 at the time of tolerance induction stimulates Th1 differentiation, but does not promote antigen-specific T cell proliferation. Conversely, inhibiting CTLA-4 engagement during anergy induction reverses the block in T cell proliferation, but does not promote fun Th1 differentiation. T cells exposed to tolerogenic antigen in the presence of both IL-12 and anti-CTLA-4 antibody are not energized, and behave identically to T cells which have encountered immunogenic antigen. These. results suggest that two processes contribute to the induction of anergy in vivo; CTLA-4 engagement, which leads to a block in the ability of T cells to proliferate to antigen, and the absence of a prototypic inflammatory cytokine, IL-12, which prevents the differentiation of T cells into Th1 effector cells. The combination of IL-12 and anti-CTLA-4 antibody is sufficient to convert a normally tolerogenic stimulus to an immunogenic one.

17/7/5 (Item 5 from file: 5)

13453822 BIOSIS NO.: 199699087882
CTLA-4 ligation blocks CD28-dependent T cell activation
AUTHOR: Walunas Theresa L; Bakker Christina Y; Bluestone Jeffrey A (Reprint)
AUTHOR ADDRESS: Ben May Inst. Cancer Res., MC1089, Univesity Chicago, 5841 S. Maryland, Chicago, IL 60637, USA**USA
JOURNAL: Journal of Experimental Medicine 183 (6): p2541-2550 1996
1996
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CTLA-4 is a CD28 homologue believed to be a negative regulator of T cell function. However, the mechanism of this downregulatory activity is not well understood. The present study was designed to examine the effect of CTLA-4 ligation on cytokine production, cell survival, and cell cycle progression. The results demonstrate that the primary effect of CTLA-4 ligation is not the induction of ***apoptosis*** . Instead, CTLA-4 signaling blocks IL-2 production, IL-2 receptor expression, and cell cycle progression of activated T cells. Moreover, the effect of CTLA-4 signaling was manifested after initial T cell activation. Inhibition of IL-2 receptor expression and cell cycle progression was more pronounced at late (72 h) time points after initial activation. The effects of anti-CTLA-4 mAbs were most apparent in the presence of optimal CD28-mediated co-stimulation consistent with the finding that CTLA-4 upregulation was CD28-dependent. Finally, the addition of

exogenous IL-2 to the cultures restored IL-2 receptor expression and T cell proliferation. These results suggest that CTLA-4 signaling does not regulate cell survival or responsiveness to IL-2, but does inhibit CD28-dependent IL-2 production.

17/7/6 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07900450 EMBASE No: 1999374235
CTLA-4 blockade reverses CD8sup + T cell tolerance to tumor by a CD4sup + T cell- and IL-2-dependent mechanism
Shrikant P.; Khoruts A.; Mescher M.F.
M.F. Mescher, Center for Immunology, Dept. of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN 55455 United States
AUTHOR EMAIL: mesch001@maroon.tc.umn.edu
Immunity (IMMUNITY) (United States) 1999, 11/4 (483-493)
CODEN: IUNIE ISSN: 1074-7613
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 46

A tumor-specific CD8sup + T cell response was studied using adoptive transfer of OT-I TCR transgenic cells. Upon i.p. challenge with E.G7 tumor, OT-I cells undergo CD4sup + T cell-independent expansion at the tumor site and develop lytic function. Before tumor elimination, however, they leave the peritoneal cavity (PC) and appear in the LN and spleen where they exhibit 'split anergy' and cannot further proliferate to antigen. Administering anti- CTLA-4 mAb early caused sustained OT-1 expansion in the PC, and late administration caused the OT-I cells to return to the PC and further expand; in both cases, tumor was controlled. These effects required CD4sup + T cells and IL-2 and appear to result from reversal of the nonresponsive state of the CD8sup + T cells.

17/7/7 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07334769 EMBASE No: 1998196007
Long-term survival of skin allografts induced by donor splenocytes and anti-CD154 antibody in thymectomized mice requires CD4sup + T cells, interferon- gamma, and CTLA4
Markees T.G.; Phillips N.E.; Gordon E.J.; Noelle R.J.; Shultz L.D.; Mordes J.P.; Greiner D.L.; Rossini A.A.
A.A. Rossini, Diabetes Division, University of Massachusetts Med. School, 373 Plantation Street, Worcester, MA 01605 United States
AUTHOR EMAIL: Aldo.Rossini@ummed.edu
Journal of Clinical Investigation (J. CLIN. INVEST.) (United States) 01 JUN 1998, 101/11 (2446-2455)
CODEN: JCINA ISSN: 0021-9738
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 60

Treatment of C57BL/6 mice with one transfusion of BALB/c spleen cells and anti-CD154 (anti-CD40-ligand) antibody permits BALB/c islet grafts to survive indefinitely and BALB/c skin grafts to survive for ~ 50 d without further intervention. The protocol induces long-term allograft survival, but the mechanism is unknown. We now report: (a) addition of thymectomy to the protocol permitted skin allografts to survive for > 100 d, suggesting

that graft rejection in euthymic mice results from thymic export of alloreactive T cells. (b) Clonal deletion is not the mechanism of underlying long-term graft survival, as recipient thymectomized mice were immunocompetent and harbor alloreactive T cells. (c) Induction of skin allograft acceptance initially depended on the presence of IFN-gamma, CTLA4, and CD4sup + T cells. Addition of ***anti*** - ***CTLA4*** or anti-IFN-gamma mAb to the protocol was associated with prompt graft rejection, whereas anti-IL-4 mAb had no effect. The role of IFN-gamma was confirmed using knockout mice. (d) Graft survival was associated with the absence of IFN-gamma in the graft. (e) Long-term graft maintenance required the continued presence of CD4sup + T cells. The results suggest that, with modification, our short-term protocol may yield a procedure for the induction of long-term graft survival without prolonged immunosuppression.

17/7/8 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07254566 EMBASE No: 1998127892
CTLA-4 regulates tolerance induction and T cell differentiation in vivo
Walunas T.L.; Bluestone J.A.
Dr. J.A. Bluestone, MC1089, 5841 South Maryland Avenue, Chicago, IL 60637 United States
AUTHOR EMAIL: jbluest@immunology.uchicago.edu
Journal of Immunology (J. IMMUNOL.) (United States) 15 APR 1998, 160/8 (3855-3860)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 35

Cytotoxic T lymphocyte Ag-4 (CTLA-4; CD152) is an important T cell regulatory molecule. In vitro experiments have shown that the blockade of signals through CTLA-4 augments T cell expansion, while CTLA-4 cross-linking results in decreased T cell proliferation due to decreased IL-2 production. However, less is known about the role of CTLA-4 in regulating an ongoing immune response. In this study, we examined the role of CTLA-4 in the expansion, decline, tolerization, and differentiation of T cells following treatment with staphylococcal enterotoxin B (SEB). Anti-CTLA-4 treatment resulted in increased numbers of SEB-reactive T cells and blockade of subsequent ***tolerance*** induction. Further examination of the SEB-reactive cells from anti-CTLA -4-treated mice demonstrated that both the CD4sup + and CD8sup + Vbeta8sup + T cells produced IL-4, providing evidence that not only do signals through CTLA-4 regulate T cell-tolerizing events, but they also play an important role in the differentiation of T cells in vivo.

17/7/9 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

07254541 EMBASE No: 1998127867
T:T antigen presentation by activated murine CD8sup + T cells induces anergy and apoptosis
Chai J.-G.; Bartok I.; Scott D.; Dyson J.; Lechler R.
Dr. R. Lechler, Department of Immunology, Hammersmith Hospital, Imperial College of Sci., Tech./Med., Du Cane Road, London W12 United Kingdom
AUTHOR EMAIL: riechler@rpms.ac.uk
Journal of Immunology (J. IMMUNOL.) (United States) 15 APR 1998, 160/8

(3655-3665)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 65

Using an IL-2-secreting, noncytolytic, H-Y-specific, CD8sup + T cell clone, the functional consequences of Ag presentation by T cells to T cells were investigated. Incubation of the T cells with H-Y-soluble peptide led to nonresponsiveness to Ag rechallenge. This was due to the simultaneous induction of apoptosis, involving approximately 40% of the T cells, and of anergy in the surviving cells. These effects were strictly dependent upon bidirectional T:T presentation, in that exposure of C6 cells to peptide- pulsed T cells from the same clone induced proliferation but not ***apoptosis*** or anergy. The inhibitory effects of T:T presentation were not due to a lack of costimulation, since the T cells expressed levels of CD80 and CD86 higher than those detected on cultured dendritic cells and equipped them to function as efficient APCs for primary CD8sup + T cell responses. Following incubation with soluble peptide, CD80 expression increased, and high levels of CTLA-4 (CD152) expression were induced. Although addition of anti-CTLA-4 Ab augmented proliferation in response to soluble peptide, no protection from apoptosis or anergy was observed. Neither Fas nor TNF-alpha was expressed/produced by the C6 cells, and coligation of MHC class I molecules and TCR failed to reproduce the effects of T:T presentation. Taken together, these data suggest that T:T Ag presentation induces anergy and apoptosis in murine CD8sup + T cells and may reflect the regulatory consequences of T:T interactions in the course of clonal expansion in vivo.

17/7/10 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

07195012 EMBASE No: 1998083489
Cutting edge: CTLA-4 ligation delivers a unique signal to resting human CD4 T cells that inhibits interleukin-2 secretion but allows bcl-X(L) induction
Blair P.J.; Riley J.L.; Levine B.L.; Lee K.P.; Craighead N.; Francomano T.; Perfetto S.J.; Gray G.S.; Carreno B.M.; June C.H.
Dr. C.H. June, Immune Cell Biology Program (061), Naval Medical Research Institute, 8901 Wisconsin Avenue, Bethesda, MD 20889-5607 United States
AUTHOR EMAIL: juneC@nmripo.nmri.nnmc.navy.mil
Journal of Immunology (J. IMMUNOL.) (United States) 1998, 160/1 (12-15)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 27

We have assessed the functional effects of a panel of CTLA-4 mAbs on resting human CD4sup + T cells. Our results demonstrate that some CTLA-4 mAbs can inhibit proliferative responses of resting CD4sup + cells and cell cycle transition from Ginf 0 to Ginf 1. The inhibitory effects of CTLA-4 were evident within 4 h, at a time when cell surface CTLA-4 expression remained undetectable. Other CTLA-4 mAbs had no detectable inhibitory effects, indicating that binding of Ab to CTLA-4 alone is not sufficient to mediate down-regulation of T cell responses. Interestingly, while IL-2 production was shut off, inhibitory anti-CTLA-4 mAbs permitted induction and expression of the cell survival gene bcl-X(L). Consistent with this observation, cells remained viable and apoptosis was not detected after CTLA-4 ligation.

17/7/11 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

07173182 EMBASE No: 1998055992
Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) regulates the unfolding of autoimmune diabetes
Luhder F.; Hoglund P.; Allison J.P.; Benoist C.; Mathis D.
Dr. D. Mathis, IGBMC, 1 rue Laurent Fries, 67404 Illkirch Cedex France
AUTHOR EMAIL: cbdm@igbmc.u-strasbg.fr
Journal of Experimental Medicine (J. EXP. MED.) (United States) 02 FEB 1998, 187/3 (427-432)
CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32

Evidence has been accumulating that shows that insulin-dependent diabetes is subject to immunoregulation. To determine whether cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is involved, we injected anti-CTLA- 4 mAb into a TCR transgenic model of diabetes at different stages of disease. When injected into young mice, months before they would normally become diabetic, anti-CTLA-4 induced diabetes rapidly and essentially universally; this was not the result of a global activation of T lymphocytes, but did reflect a much more aggressive T cell infiltrate in the pancreatic islets. These effects were only observed if anti-CTLA-4 was injected during a narrow time window, before the initiation of insulitis. Thus, engagement of CTLA-4 at the time when potentially diabetogenic T cells are first activated is a pivotal event; if engagement is permitted, invasion of the islets occurs, but remains quite innocuous for months, if not, insulitis is much more aggressive, and diabetes quickly ensues.

17/7/12 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12179813 PMID: 10590254
The role of CTLA-4 in tolerance induction and ttigen administration cell differentiation in experimental autoimmune encephalomyelitis: i. v. antigen administration.
Ratts R B; Arredondo L R; Bittner P; Perrin P J; Lovett-Racke A E; Racke M K
Department of Neurology, Washington University School of Medicine, St Louis, MO 63110, USA.
International immunology (ENGLAND) Dec 1999, 11 (12) p1889-96, ISSN 0953-8178--Print Journal Code: 8916182
Contract/Grant Number: R01-NS-37513; NS; NINDS; R29-AI-43296; AI; NIAID
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM.
Record type: MEDLINE; Completed
Interactions between B7 molecules on antigen-presenting cells and CTLA-4 on T cells have been shown to be important in establishing ***tolerance*** . In the present study, we examined the kinetics of tolerance induction following i.v. administration of myelin basic protein (MBP) Ac1-11 in mice transgenic for a TCR V(beta)8.2 gene derived from an encephalitogenic T

cell clone specific for MBP Ac1-11. Examination of the lymph node cell (LNC) response 10 days after antigen administration demonstrated an accentuation of i.v. ***tolerance*** induction with ***anti*** - ***CTLA*** -4
blockade. Anergy was induced in splenocytes by i.v. antigen administration as shown by a decrease in MBP-specific proliferation and IL-2 production, and ***anti*** - ***CTLA*** -4 potentiated this effect. In addition, i.v. antigen plus anti-CTLA-4 and complete Freund's adjuvant was not encephalitogenic. Interestingly, i.v. ***tolerance*** (a single injection) did not inhibit experimental autoimmune encephalomyelitis (EAE) and ***anti*** - ***CTLA*** -4 administration did not alter this phenotype. These results suggest that while the majority of MBP-specific T cells are tolerized by i.v. antigen and that this process is potentiated by anti-CTLA -4 administration, a population of T cells remains that is quite efficient in mediating EAE.
Record Date Created: 20000124
Record Date Completed: 20000124

17/7/13 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11937962 PMID: 9763603
Cytotoxic T lymphocyte antigen 4 is induced in the thymus upon in vivo activation and its blockade prevents anti-CD3-mediated depletion of thymocytes.
Cilio C M; Daws M R; Malashicheva A; Sentman C L; Holmberg D
Department for Cell and Molecular Biology, Umea University, S-901 87 Umea, Sweden.
Journal of experimental medicine (UNITED STATES) Oct 5 1998, 188 (7) p1239-46, ISSN 0022-1007--Print Journal Code: 2985109R
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The development of a normal T cell repertoire in the thymus is dependent on the interplay between signals mediating cell survival (positive selection) and cell death (negative selection or death by neglect). Although the CD28 costimulatory molecule has been implicated in this process, it has been difficult to establish a role for the other major costimulatory molecule, cytotoxic T lymphocyte antigen (CTLA)-4. Here we report that in vivo stimulation through the T cell receptor (TCR)-CD3 complex induces expression of CTLA-4 in thymocytes and leads to the association of CTLA-4 with the SH2 domain-containing phosphatase (SHP)-2 tyrosine phosphatase. Moreover, intrathymic CTLA-4 blockade dramatically inhibits anti-CD3-mediated depletion of CD4+CD8+ double positive immature thymocytes. Similarly, anti-CD3-mediated depletion of CD4+CD8+ double positive cells in fetal thymic organ cultures could also be inhibited by ***anti*** - ***CTLA*** -4 antibodies. Thus, our data provide evidence for a role of CTLA-4 in thymic selection and suggest a novel mechanism contributing to the regulation of TCR-mediated selection of T cell repertoires.
Record Date Created: 19981116
Record Date Completed: 19981116

17/7/14 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11743770 PMID: 9558065
T:T antigen presentation by activated murine CD8+ T cells induces anergy and ***apoptosis*** .
Chai J G; Bartok I; Scott D; Dyson J; Lechler R
Department of Immunology, Hammersmith Hospital, Imperial College of Science, Technology, and Medicine, London, United Kingdom.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Apr 15 1998, 160 (8) p3655-65, ISSN 0022-1767--Print Journal Code: 2985117R
Publishing Model Print
Document type: In Vitro; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Using an IL-2-secreting, noncytolytic, H-Y-specific, CD8+ T cell clone, the functional consequences of Ag presentation by T cells to T cells were investigated. Incubation of the T cells with H-Y-soluble peptide led to nonresponsiveness to Ag rechallenge. This was due to the simultaneous induction of apoptosis, involving approximately 40% of the T cells, and of anergy in the surviving cells. These effects were strictly dependent upon bidirectional T:T presentation, in that exposure of C6 cells to peptide-pulsed T cells from the same clone induced proliferation but not ***apoptosis*** or anergy. The inhibitory effects of T:T presentation were not due to a lack of costimulation, since the T cells expressed levels of CD80 and CD86 higher than those detected on cultured dendritic cells and equipped them to function as efficient APCs for primary CD8+ T cell responses. Following incubation with soluble peptide, CD80 expression increased, and high levels of CTLA-4 (CD152) expression were induced. Although addition of anti-CTLA-4 Ab augmented proliferation in response to soluble peptide, no protection from apoptosis or anergy was observed. Neither Fas nor TNF-alpha was expressed/produced by the C6 cells, and coligation of MHC class I molecules and TCR failed to reproduce the effects of T:T presentation. Taken together, these data suggest that T:T Ag presentation induces anergy and apoptosis in murine CD8+ T cells and may reflect the regulatory consequences of T:T interactions in the course of clonal expansion in vivo.
Record Date Created: 19980504
Record Date Completed: 19980504

17/7/15 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11739136 PMID: 9551948
CTLA-4 ligation delivers a unique signal to resting human CD4 T cells that inhibits interleukin-2 secretion but allows Bcl-X(L) induction.
Blair P J; Riley J L; Levine B L; Lee K P; Craighead N; Francomano T; Perfetto S J; Gray G S; Carreno B M; June C H
Naval Medical Research Institute, Bethesda, MD 20889-5607, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Jan 1 1998, 160 (1) p12-5, ISSN 0022-1767--Print Journal Code: 2985117R
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, Non-P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We have assessed the functional effects of a panel of CTLA-4 mAbs on resting human CD4+ T cells. Our results demonstrate that some CTLA-4 mAbs can inhibit proliferative responses of resting CD4+ cells and cell cycle

transition from G0 to G1. The inhibitory effects of CTLA-4 were evident within 4 h, at a time when cell surface CTLA-4 expression remained undetectable. Other CTLA-4 mAbs had no detectable inhibitory effects, indicating that binding of Ab to CTLA-4 alone is not sufficient to mediate down-regulation of T cell responses. Interestingly, while IL-2 production was shut off, inhibitory anti-CTLA-4 mAbs permitted induction and expression of the cell survival gene bcl-X(L). Consistent with this observation, cells remained viable and apoptosis was not detected after CTLA-4 ligation.
Record Date Created: 19980507
Record Date Completed: 19980507

17/7/16 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

124229989 CA: 124(17)229989f PATENT
Ligands for induction of antigen specific apoptosis in T cells
INVENTOR(AUTHOR): Gribben, John G.; Freeman, Gordon J.; Nadler, Lee M.; Rennert, Paul; Jellis, Cindy L.; Greenfield, Edward; Gray, Gary S.
LOCATION: USA
ASSIGNEE: Repligen Corp.; Dana Farber Cancer Institute
PATENT: PCT International ; WO 9533770 A1 DATE: 951214
APPLICATION: WO 95US6726 (950602) *US 253783 (940603)
PAGES: 86 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: C07K-014/705A; C07K-016/28B; A61K-039/395B; A61K-038/17B
DESIGNATED COUNTRIES: AU; CA; JP DESIGNATED REGIONAL: AT; BE; CH; DE; DK ; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA215003 Immunochemistry
IDENTIFIERS: T cell antigen specific apoptosis ligand, CTLA4 monoclonal antibody T cell apoptosis, graft rejection autoimmune bone marrow transplant
DESCRIPTORS:
Lymphocyte,T-cell...
apoptosis; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Animal cell line...
B lymphoblastoid; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune disease
Lymphoblast,B-cell...
cell line; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Antibodies...
chimeric or humanized; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune di
Proteins,specific or class, fusion products...
CTLA4-containing; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Antigens,CTLA-4 (cytotoxic T-lymphocyte-activating, 4)...
ligand; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Allergens... Allergy... Antibodies,monoclonal... Antigen receptors,TCR (T-cell antigen receptor)... Antigens... Antigens,auto-... Antigens,B 7.2

... Antigens,B7/BB-1... Antigens,CD28... Antigens,CD3... Apoptosis... Autoimmune disease... Bone marrow,transplant... Lymphokine and cytokine receptors,interleukin 2... Lymphokines and Cytokines,interleukin 2... Lymphokines and Cytokines,T-cell growth factor... Receptors,interleukin-2 ... Receptors,TCR (T-cell antigen receptor)... Transplant and Transplantation,graft-vs.-host reaction...
monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
Transplant and Transplantation...
rejection; monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
CAS REGISTRY NUMBERS:
174777-52-7 174777-53-8 monoclonal anti-CTLA4 antibodies and fragments and CTLA4 ligand for induction of antigen-specific apoptosis in T cells for preventing graft rejection or allergy or autoimmune diseases
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